From:	Subramaniam, Ravi [/O=EXCHANGELABS/OU=EXCHANGE ADMINISTRATIVE GROUP (FYDIBOHF23SPDLT)/CN=RECIPIENTS/CN=E738F9D27062486E9047184B867FD968-SUBRAMANIAM, RAVI]
Sent:	4/24/2014 11:55:11 PM
To:	Kraft, Andrew [kraft.andrew@epa.gov]; Glenn, Barbara [glenn.barbara@epa.gov]
Subject:	CONFIDENTIAL: email from Andersen

Andrew/ Barbara:

As with the past workshop, tension appears to be building up a bit as we near the date. Before we go any further, I would like you to keep this to yourself and not share with anyone until we have decided it needs to be. As I mentioned to you, I encouraged Paul Schlosser to share the background to his "sequestration" hypothesis with the presenters and the co-chair with a copy to ICF. I did this following the planning discussion we had with everyone where we briefly mentioned the question of how much endogenous formaldehyde was available. This has elicited an angry response from Mel. Note that it was sent only to me and Paul.

I am scheduled to talk to Mel tomorrow at 11:00 to discuss his concern. Originally I had thought I would appraise you of this only after my conversation with him, but I am thinking now it might help talking with either of you. If it is OK to call tomorrow, please let me know when.

Ravi.

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From: Mel Andersen [mailto:MAndersen@thehamner.org]
Sent: Thursday, April 24, 2014 10:12 AM
To: Schlosser, Paul; Subramaniam, Ravi
Subject: RE: Formaldehyde Workshop: Session 1 Planning Call

Paul/Ravi,

I found this e-mail somewhat irritating. You seem to be moving away from the purported rationale for the meeting to a position where you want the panel to weigh in on assessing their comfort with your unpublished musings about formaldehyde.

As you know, The Hamner has been involved in developing PK models that account for exogenous and endogenous input of formaldehyde for the past 5 years. Some initial work appeared in our 2010 paper trying to link gene expression, toxicity and preliminary PK structures for both inhaled formaldehyde and endogenous production to predict protein cross-links (Andersen et al., Toxicol. Sci., 2010). With Jerry Campbell taking the lead, we continued the PK modeling work using newer adduct data from Jim's papers and have reported these results at the SRA meeting last year (Clewell et al, (2013), "Pharmacokinetics of Inhaled Formaldehyde and the Impact of Endogenous Levels"). We have delayed publication of the our recent PK modeling work pending availability of more complete data sets coming from Jim Swenberg's team. In addition, we have worked to develop CFD models that account for endogenous formaldehyde in a paper in press from Jeff Schroeter et al., Toxicol. Sci., 138, 412-424, 2014. As the development of these model structures move forward, we are refining ideas about pools of formaldehyde and cellular compartmentalization — especially in relation to cytosolic and nuclear compartments.

We will be completing our PK modeling work in the next few months. The published work will be available for general review and discussion by US EPA and by others. Nonetheless, we hope it will be used in EPA deliberations about endogenous formaldehyde, but EPA needs it in an appropriate form to assess model structure and performance and to consider if you agree with description of formaldehyde in tissues. I would be pleased to have a conversation about key ideas – most tissue formaldehyde is reversibly bound with various nucleophiles, the reactivity in tissue is likely due to reactions with the formaldehyde acetal and displacement of water by other nucleophiles, the early formaldehyde assays assessed levels of loosely bound formaldehyde that can be reacted irreversibly to form hydrazone derivatives. The relevant concentration in specific compartments is more likely to be this pool of "bound", but available formaldehyde rather than free CH_2O. My experience as a chemist and biochemist strongly support this model structure.

My point in this longish e-mail is a question about the meeting itself. What is it that you want covered in these sessions? Published papers with specific information, work in progress that has been reported, but not yet finalized, or comment on some set of unpublished calculations?

I am interested in your response to this e-mail and your opinions about whether you should also send some of this material to the presenters and discussants? I actually don't think any of this should be going to the panel members and discussants at this late stage. However, I feel that your distribution of the unpublished musings biases the panel inappropriately.

Mel

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From: Schlosser, Paul [mailto:Schlosser.Paul@epa.gov]
Sent: Thursday, April 24, 2014 9:15 AM
To: Wignall, Jessica; Subramaniam, Ravi; Mel Andersen; Edna Mangum; Appling, Dean; Lisa Peterson; Ross, Jeff; Martyn Smith; James Swenberg
Cc: kim.osborn@icfi.com; Malloy, Maureen; Sharp, Codi
Subject: RE: Formaldehyde Workshop: Session 1 Planning Call

Colleagues,

Ravi recalled that I'd done an analysis based on some of Dr. Swenberg's data in combination with the formaldehyde inhalation dosimetry model of Conolly et al. (2000) to contrast the levels of N^2-hydroxymethyl-deoxyguanine (dG) adducts with what's known or can be estimated for endogenous vs. exogenous levels, and asked that I send it around. I've attached the piece. It's just over 2 pages, though a bit dense.

Part of this may be trumped by recent data that Jim mentioned on the phone.

In short the Conolly et al. model used observed DNA-protein-crosslink (DPX) data and a rate constant for DPX formation from in vitro experiments to effectively estimate the nasal tissue levels of HCHO at various exposure levels. I then extended the model to predict dG formation and clearance (assuming formation is proportional to HCHO levels and clearance is first-order), calibrating the extended model to Jim's dG data from 6-h exposures. I then used the model to predict what dG levels would be given continuous HCHO exposure or a long-tern 5 d/wk, 6 h/d pattern.

Also, I can use the model to back calculate what level of "free" HCHO must be in the cells to be consistent with the observed endogenous dG levels. As stated, reported/measured endogenous formaldehyde levels are ~ 400 uM, but if that formaldehyde was as available to form dG as the exogenous formaldehyde in Jim's experiments, then the endogenous dG levels should be ~ 40 times higher than observed. Put another way, the endogenous dG levels, based on this modeling, are only consistent with a "free" endogenous HCHO level of 10.4 uM, not 400 uM. This much lower level of "free" endogenous formaldehyde is also much more consistent with the relative potency of exogenous vs. endogenous formaldehyde in forming tumors in the rat nose. So this analysis suggests that over 97% of the measurable formaldehyde is reversibly bound or sequestered in a way that keeps it from reacting with DNA ... and causing tumors.

While the mathematical models used here are anchored in data, they are clearly extrapolations. As you are putting together your talks, any information your could provide to support, refine, or negate these predictions would be helpful!

Thanks,
-Paul

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